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The role of initial sodium and globulin values in the prognosis prediction of patients diagnosed with colon cancer

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ABSTRACT

Aims: Early prediction of prognosis in malignancies can help determine life expectancy and take necessary further measures accordingly. There is no consensus on using any biomarker in predicting prognosis in colon cancer cases. A study reported that the sodium/globulin ratio is a valuable biomarker in predicting the prognosis of gastric cancer. This study aimed to investigate the role of baseline sodium, globulin, and sodium/globulin ratio in the prediction of prognosis and survival in colon cancer cases.

Methods: The files of patients diagnosed with colon cancer who applied to Kırıkkale University Faculty of Medicine Medical Oncology Clinic between January 1, 2015, and December 31, 2020, were retrospectively analyzed. The relationship between the clinical and laboratory characteristics of the cases and their progression and survival were investigated.

Results: 140 patients diagnosed with colon cancer were included in the study (82 men, 58 women). The average age at diagnosis was 64.1±12.6 years, 99.3% of them were adenocarcinoma, and 32.9% of them were stage 4 cancers. It was determined that 42.1% of the patients died (average survival time 54.0±3.2 months), and progression developed in 18.6% during the study period. The average baseline sodium/globulin ratio was 51.10±8.70. No significant correlation was found between initial serum sodium level, globulin level, sodium/globulin ratio, survival time, and progression status ($p>0.05$). Baseline serum globulin level showed a weak negative correlation with both progression-free and overall survival time ($r=-0.23$, $p<0.05$ and $r=-0.24$, $p<0.05$, respectively), while the sodium/globulin ratio showed a weak positive correlation with progression-free survival time ($r=0.26$, $p<0.01$) and overall survival time ($r=0.25$, $p<0.01$). The ROC curve analysis determined that initial serum sodium and globulin levels and sodium/globulin ratio were not predictive of progression and survival at any cut-off point ($p>0.05$).

Conclusion: Although baseline serum sodium level, globulin level, and serum sodium/globulin ratio were weakly correlated with progression-free and overall survival time of patients diagnosed with colon cancer, they were not valuable in predicting progression and survival.

Keywords: Colon cancer, prognosis, sodium, globulin.

INTRODUCTION

Colorectal cancer is the third most frequently diagnosed malignancy and the second most deadly malignancy in both genders. The etiology of colorectal cancer includes both environmental and genetic risk factors. The incidence of new cases and mortality have declined in recent years, except for young adults (less than 50 years old), due to the increase in cancer screening and progressing treatment methods. Colon cancer (Kca) can be presented as sporadically (70%), familial (20%), and hereditary 10%).[1-3] Sporadic Kca mostly depends on environmental factors and is diagnosed after an average of 50 years of age. The sporadic type is diagnosed at a younger age (less than 50) and is separate from others. About 20% of the cases are familial Kca without any hereditary syndrome. The most common hereditary colorectal cancer syndromes are familial adenomatous polyposis (FAP) and Lynch syndrome (Hereditary non-polyposis colorectal cancer [HNPCC]).[4,5]

Inflammatory bowel diseases (IBD), especially ulcerative colitis, significantly correlate with Kca. The incidence of Kca is 0.5% per year between 10 and 20 years after diagnosis of IBD and 1% per year after that. The probability of risk Kca is 30% in the fourth decade after diagnosing patients with pancolitis. Crohn's disease may increase the risk of Kca, especially if present in the ileocolic region. Those who receive abdominal radiation (more than 30 Gy) due to childhood malignancy are at increased risk of colorectal cancer. It is recommended

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that these patients be screened after 10 years or at the age of 35. Other diseases increasing the risk of colorectal cancer; include diabetes mellitus, insulin resistance, uncontrolled acromegaly, and long-term immunocompromised kidney transplant patients.[6,7]

Epidemiological study results refer to environmental and lifestyle effects for colorectal cancer. Moderately increased risk of colorectal cancer has been reported with obesity, red/processed meat, tobacco, alcohol, androgen deprivation therapy, and cholecystectomy. On the other hand, extensive population studies suggested that physical activity, diet (fruits and vegetables, fiber food, starch, fish), vitamin supplements (folic acid, pyridoxine B6, calcium, vitamin D, magnesium), garlic, coffee, and drugs (aspirin, non-steroidal anti-inflammatory drugs, postmenopausal hormone replacement therapy, statins, bisphosphonate and angiotensin inhibitors) may be protective in terms of colorectal cancer.[8-10]

Colorectal cancers are the third most common cancer in both genders in Turkey.[9] Inflammation is often associated with cancer development and progression.[10] Systemic inflammation is present preoperatively in about 20-40% of colorectal cancer patients, indicating a poor prognosis.[11] Electrolyte disturbances in cancer patients are also associated with a poor prognosis.[12] In patients with cancer, hyponatremia has been associated with a more extended hospitalization period and higher mortality.[13] In patients with gastric cancer, serum sodium, and globulin levels may reflect electrolyte hemostasis and inflammatory status; a study considered that sodium/globulin ratio (SGO) may be more significant in reflecting prognosis than sodium and globulin alone. SGO is an independent and reliable prognostic factor that can predict sensitivity to chemotherapy more effectively than sodium or globulin alone has been reported as far as we know, there is no study in the literature examining the relationship between SGO and prognosis and survival in patients diagnosed with colon cancer.[14] In order to improve survival rates in this patient group, new and effective prognostic factors need to be determined. This study was intended to research the place of sodium globulin levels and ratios at the time of diagnosis in the prediction of prognosis in cases diagnosed with colon cancer.

METHODS

This thesis study was conducted by the colon cancer patients who applied to the Oncology Clinic of Kırıkkale University Faculty of Medicine between January 1, 2015, and December 31, 2020, retrospectively as an internal medicine specialization thesis. The study was approved by the Kırıkkale University Non-Interventional Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021.06.14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Cases diagnosed with colon cancer within a specified five-year date range were included in the study. The G Power 3.1.9.2 package program calculates the study's power and sample. Accordingly, Considering the Zhang et al. study's determined results in the analysis that was conducted, When the research's power was calculated to be 0.80, and the margin of error was calculated to be 0.05 (alpha), it was decided that 126 subjects should be included in the study. Considering the 10% possible data loss, 140 people were included.[14]

Inclusion Criteria

- Having been diagnosed with colon cancer histopathologically,
- Being at least 18 years old,
- Possess measurable sodium and globulin levels three months after diagnosis,
- Receiving at least six months of follow-up care in our hospital,

Exclusion Criteria

- Stage 3 and later chronic kidney disease, cirrhosis, liver failure, advanced heart failure, illnesses of the central nervous system, hypothyroidism, malnutrition, the presence of an active infection, the presence of a chronic inflammatory disease, nephrotic syndrome, sepsis, use of diuretics such as serum sodium, and conditions that can affect plasma protein levels
- Being younger than 18

Data Collection

The parameters examined:

- Patient characteristics (age, gender, smoking status, additional diseases)
- Diagnostic characteristic (date of first diagnosis, histopathologic subtype, stage)
- Current state of health (presence of operation, presence and date of mortality, presence and date of progression)
- Biochemical parameters (globulin, albumin, total protein, sodium, potassium, hemoglobin, platelet, leukocyte, CRP, ALT, creatinine, GFR, and globulin)

Working Procedure

One investigator used the hospital registry system and patient files to record the data of the cases retrospectively, and patients were split into two groups: dead and (ii) alive. The patient characteristics, diagnostic, and biochemical parameters will be compared between these two groups. Serum sodium, globulin levels, and SGO at the time of diagnosis were some of the parameters examined. Progression and mortality, which are related to prognosis, were also examined.

Statistical Analysis

Statistics were performed using the SPSS (Statistical Package for Social Sciences) 25 package program after the data collected during the research were entered into the database. The chi-square test was used to analyze relationships between categorical data, described with their frequencies and percentages. The average, standard deviation, median, minimum, and maximum values for continuous variables are shown.

The Shapiro-Wilk test assessed whether continuous variables followed a normal distribution. In the evaluation of continuous numerical variables between two independent groups, in the presence of normal distribution, independent samples were checked with a t-test. Mann Whitney U test was used in cases where normal distribution was not achieved. Since the survival values were not normally distributed, the correlation relationship with other numerical parameters was checked with the Spearman Correlation test.

ROC (receiver operating characteristic) analysis was used to assess the predictability of numerical survival parameters. The Kaplan-Meier test was used for risk and survival analysis, and the Long-Rank test was used to present the results. $p<0.05$ was considered significant.

RESULTS

Descriptive Features of the Cases

Demographic and clinical characteristics of 140 patients diagnosed with colon cancer (58 females, 82 males) who were followed up at Kırıkkale University Faculty of Medicine Medical Oncology Clinic between January 1, 2015, and December 31, 2020, are shown in Table 1. The average age of diagnosis of the cases was 64.1±12.6 (19-89) years. Histopathological results were 99.3% adenocarcinoma. 32.9% of the subjects had stage 4 cancer, 95.7% had received chemotherapy, and 93.6% had been operated on. It was determined that 59 (42.1%) patients died, and 81 (18.6%) progressed.

Table 1. Demographic and clinical characteristics of patients with colon cancer (n=140)

	n	%
Age (year)	64.1±12.6*	
Gender n(%)		
Female	58	41.4
Male	82	58.6
Smoking		
Smoker	101	72.1
Non-smoker	39	27.9
Diabetes		
No	101	72.1
Yes	39	27.9
Hypertension		
No	83	59.3
Yes	57	40.7
Coronary artery disease		
No	121	86.4
Yes	19	13.6
Histopathology		
Adenocancer	139	99.3
Neuroendocrine tumor	1	0.7
Stage		
1	19	13.6
2	33	23.6
3	42	30
4	46	32.9
Chemotherapy		
No	6	4.3
Yes	134	95.7
Operation		
No	9	6.4
Yes	131	93.6
Survival		
Alive	81	57.9
Deceased	59	42.1
Progression		
No	114	81.4
Yes	26	18.6

Data are given as numbers (percentage) or *Average±standard deviation.

In the laboratory values at the beginning of the follow-up of patients with colon cancer, serum sodium was 139.4±3.3, serum globulin was 2.8±0.5, and sodium/globulin ratio was 51.1±8.7.

Analysis of Parameters Associated with Overall Survival

A comparison of demographic and clinical characteristics when colon cancer patients are grouped as living and dying according to survival status is shown in Table 2.

Table 2. Demographic and clinical characteristics of colon cancer patients according to survival (n=140)

Parameter	Survival status		p
	Alive (n=81)	Deceased (n=59)	
Age (year)	64.0±10.7	64.1±15.0	0.972*
Gender			0.616
Female	35 (43.2%)	23 (39.0%)	
Male	46 (56.8%)	36 (61.0%)	
Smoking			0.328
Non-smoker	61 (75.3%)	40 (67.8%)	
Smoker	20 (24.7%)	19 (32.2%)	
Diabetes			0.190
No	55 (67.9%)	46 (78%)	
Yes	26 (32.1%)	13 (22%)	
Hypertension			0.994
No	48 (59.3%)	35 (59.3%)	
Yes	33 (40.7%)	24 (40.7%)	
Coronary artery disease			0.316
No	68 (84.0%)	53 (89.8%)	
Yes	13 (16.0%)	6 (10.2%)	
Histopathology result			0.240
Adenocancer	81 (100.0%)	58 (98.3%)	
Neuroendocrine tumor	0 (0.0%)	1 (1.7%)	
Stage			<0.001
1	16 (19.8%)	3 (5.1%)	
2	26 (32.1%)	7 (11.9%)	
3	24 (29.6%)	18 (30.5%)	
4	15 (18.5%)	31 (52.5%)	
Chemotherapy			0.655
No	4 (4.9%)	2 (3.4%)	
Yes	77 (95.1%)	57 (96.6%)	
Operation			0.025
No	2 (2.5%)	7 (11.9%)	
Yes	79 (97.5%)	52 (88.1%)	
Progression			<0.001
No	75 (92.6%)	39 (66.1%)	
Yes	6 (7.4%)	20 (33.9%)	

p: The statistical significance level of comparison between living and deceased groups (Chi-square test), * Independent samples t-test was used for comparison.

When the survival rates of all colon cancer patients according to the stages were examined, it was observed that the death rate increased significantly as the stage of colon cancer increased (p<0.001).

Laboratory and progression-free survival times according to the survival status of patients with colon cancer are shown in Table 3.

Table 3. Laboratory and progression-free survival times according to the survival status of colon cancer patients (n=140)

Parameter	Survival status		p
	Alive (n=81)	Deceased (n=59)	
Hemoglobin (g/dl)	13.7±13.9	11.9±1.7	0.309
Leucocyte (x103/mL)	7.2±2.1	7.9±2.4	0.060
Platelet (x103/mL)	291.1±97.3	321.9±134.8	0.120
C-reactive protein (mg/L)	3.6±1.4	4.0±1.0	0.155
ALT (U/L)	19.6±12.4	23.3±21.0	0.204
GFR (mL/dk/1,73 m2)	91.0±14.8	88.6±13.9	0.163
TSH (mIU/L)	1.8±0.9	2.3±0.8	0.053
CA 19-9 (U/mL)	34.2±129.8	136.3±290.7	0.005
CEA (ng/ml)	4.7±7.5	12.3±14.9	0.103
Total protein (g/dL)	7.0±0.6	6.9±0.6	0.603*
Albumin (g/dL)	4.2±0.5	4.0±0.5	0.082*
Globulin (g/dL)	2.8±0.5	2.6±0.5	0.170
Potassium (mg/dL)	4.5±0.6	4.6±0.4	0.154
Sodium (mEq/L)	139.5±3.3	139.4±3.6	0.873*
Sodium/Globulin	51.8±8.8	50.2±8.6	0.137
Urea (mg/dL)	32.2±12.9	33.4±13.4	0.695
Creatinine (mg/dL)	0.8±0.2	0.9±0.2	0.099*
Progression-free survival (month)	37.4±20.9	20.1±13.4	<0.001

ALT: Alanine Aminotransferase, CA: Cancer Antigen, CEA: Carcinoembryonic Antigen, GFR: Glomer Filtration Rate, SD: Standard Deviation, TSH: Thyroid Stimulating Hormone
Data are given as average±standard deviation.
p: The statistical significance level of comparison between living and deceased groups
* Independent samples t-test was used, Mann Whitney U test was used in other analyzes.

A comparison of overall survival times according to demographic and clinical characteristics of patients with colon cancer is given in **Table 4**. The average overall survival of all cases was 54.0±3.2 (95% CI: 47.7-60.3) months.

Table 4. Overall survival times of patients with colon cancer according to demographic and clinical characteristics (Kaplan Meier and Log-rank test) (n=140).

Parameter	n	Deceased n	Overall survival time (month) Average±SE	(%95 CI)	p
All patients	140	59	54.0±3.2	(47.7-60.3)	N/A
Age (year)					0.575
< 65	64	26	56.0±4.7	(46.7-65.2)	
≥ 65	76	33	47.4±3.2	(47.7-60.3)	
Gender					0.514
Female	58	23	57.3±4.9	(66.9-48.9)	
Male	82	36	46.2±3.1	(40.1-52.3)	
Smoking					0.324
Non-smoker	101	40	56.0±3.8	(48.6-63.4)	
Smoker	39	19	42.2±4.2	(33.9-50.5)	
Diabetes					0.159
No	101	46	50.3 ±3.8	(42.9-57.8)	
Yes	39	13	54.6±4.7	(45.4-63.8)	
Hypertension					0.959
No	83	35	52.5±4.2	(44.3-60.7)	
Yes	57	24	49.2±4.0	(41.3-57.1)	
Coronary artery disease					0.370
No	121	53	52.7±3.4	(46.0-49.5)	
Yes	19	6	47.4±5.2	(37.2-57.7)	
Progression					<0.001
No	114	39	60.0±3.6	(53.0-67.0)	
Yes	26	20	32.6±3.8	(25.3-39.9)	
Stage					<0.001
1	19	3	64.3±4.5	(55.5-73.1)	
2	33	7	71.9±5.6	(60.9-82.9)	
3	42	18	45.6±4.4	(36.9-54.3)	
4	46	31	32.5±3.3	(26.1-38.9)	
Chemotherapy					0.747
No	6	2	29.8±6.1	(17.9-41.7)	
Yes	134	57	54.2±3.3	(47.7-60.6)	
Operation					0.005
No	9	7	29.3±7.8	(14.5-44.5)	
Yes	131	52	56.4±3.3	(49.9-62.8)	

SE: Standard Error, CI: Confidence Interval

Examination of Parameters Associated with Progression-Free Survival

A comparison of demographic and clinical characteristics when patients with colon cancer are grouped according to progression-free survival is shown in **Table 5**.

The progression-free survival rates of all colon cancer patients by stage are shown in **Figure 1**. While no progression was observed in any of the stage 1 cases, it was determined that the frequency of progression increased with the increase in the stage from stage 2, and there was a statistically significant relationship between the two conditions (p=0.006).

No laboratory parameters significantly differed between patients with and without progression, including initial serum sodium, globulin levels, and sodium/globulin ratios (p>0.05). The two groups had no significant difference regarding overall survival time (p>0.05).

All cases' average progression-free survival time was 50.5±3.3 (95% CI: 44.0-57.0) months. Age, gender, smoking, presence of other diseases, and operation status were not associated with progression-free survival (p>0.05). There was a statistically significant difference in terms of progression-free survival time between stages (p=0.003); Accordingly, the progression-free survival time of stage 3 cases (p=0.001, p=0.004, respectively) and stage 4 cases (p<0.001) was statistically significantly shorter when compared with stage 1 and 2 patients.

Table 5. Demographic and clinical characteristics of patients with colon cancer according to progression-free survival (n=140)

Parameter	Progression		p
	No (n=114)	Yes (n=26)	
Age (year)	65.05±10.77	59.77±18.34	0.168*
Gender			0.325
Female	45 (39.5%)	13 (50%)	
Male	69 (60.5%)	13 (50%)	
Smoking			0.116
Non-smoker	79 (69.3%)	22 (84.6%)	
Smoker	35 (30.7%)	4 (15.4%)	
Diabetes			0.547
No	81 (71.1%)	20 (76.9%)	
Yes	33 (28.9%)	6 (23.1%)	
Hypertension			0.253
No	65 (57%)	18 (69.2%)	
Yes	49 (43%)	8 (30.8%)	
Coronary artery disease			0.765
No	99 (86.8%)	22 (84.6%)	
Yes	15 (13.2%)	4 (15.4%)	
Histopathology result			-
Adenocancer	114 (100%)	25 (96.2%)	
Neuroendocrine tumor	0 (0%)	1 (3.8%)	
Stage			0.006
1	19 (16.7%)	0 (0%)	
2	30 (26.3%)	3 (11.5%)	
3	28 (24.6%)	14 (53.8%)	
4	37 (32.5%)	9 (34.6%)	
Chemotherapy			0.232
No	6 (5.3%)	0 (0%)	
Yes	108 (94.7%)	26 (100%)	
Operation			0.239
No	6 (5.3%)	3 (11.5%)	
Yes	108 (94.7%)	23 (88.5%)	
Survival			<0.001
Alive	75 (65.8%)	6 (23.1%)	
Deceased	39 (34.2%)	20 (76.9%)	

p: The statistical significance level of comparison (Chi-square test) between groups with and without progression, * Independent samples t-test was used for comparison.

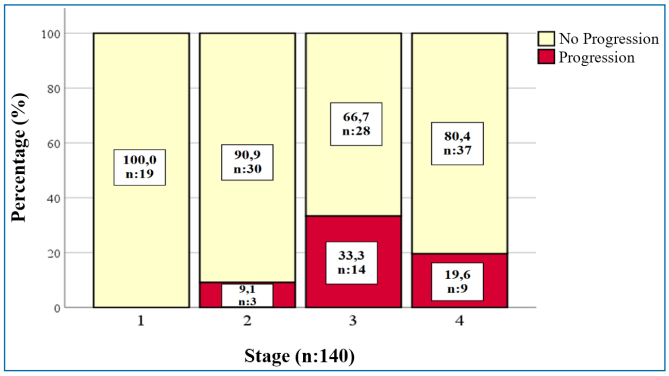

Figure 1. Progression rates according to the stage in patients with colon cancer

The progression-free survival curve by stage in patients with colon cancer is shown in **Figure 2**.

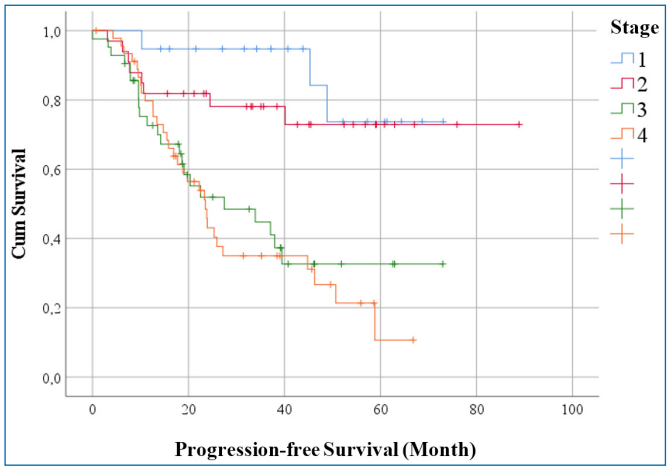

Figure 2. Progression-free survival curve according to the stage of colon cancer patients

Relation of Overall and Progression-Free Survival and Other Numerical Parameters

The relationship between overall survival and progression-free survival times and age and laboratory values in patients with colon cancer is shown in Table 15. Both overall and progression-free survival time and baseline serum ALT (r=-0.183, p=0.030, r=-0.181, p=0.033, respectively) and globulin levels (r=-0.229, p=0.006, r=-, respectively). 0.239, p=0.005) and a positive but weak correlation with sodium/globulin level (r=0.247, p=0.003, r=0.257, p=0.002, respectively).

Sodium/globulin (AUC=0.426, p=0.136), globulin (AUC=0.568, p=0.170), and sodium (AUC=0.490, p=0.838) in the ROC analysis performed to examine the predictability of sodium, globulin and sodium/globulin values for survival values were not found to be significant in terms of predicting mortality at any cut-off point.

In the ROC analysis performed to examine the predictability of sodium, globulin, and sodium/globulin values for progression, it was determined that sodium/globulin (AUC=0.496, p=0.955), globulin (AUC=0.509, p=0.889) and sodium (AUC=0.618, p=0.060) values It was determined that there was no significant value in predicting progression at any cut-off point.

DISCUSSION

Despite the developments in medicine, cancer continues to be a common and frequently fatal disease in the world. For this reason, it is crucial to diagnose possible cancer cases early and choose the optimal treatment by predicting the prognosis during diagnosis.[13,15,16] In this study, in which 140 colon cancer cases were included in our center, and the sodium and globulin levels and sodium/globulin ratio at the beginning of the follow-up were examined, the predictability of progression was found to indicate that globulin level and sodium/globulin ratio were associated with progression and survival at the end of a average follow-up of 33.2±19.1 months. It was determined that there was a weak correlation but no value in predicting survival. Among the other parameters examined, it was observed that cancer stage, CA-19-9, ALT, and operation status after colon cancer diagnosis were more strongly associated with progression and survival, and the development of progression decreased the overall survival time. However, no relationship was found between sodium and globulin levels and the sodium/globulin ratio with these parameters.

Solid cancers are generally staged according to the extent of spread in the organ they involve and the level of metastasis to other organs. Another purpose of this staging is to determine the patient's treatment and predict the prognosis. Almost all studies have shown that the cancer stage is closely related to survival.[17,18]

Ulanja et al.[17] in their study examining the parameters affecting survival in colon cancer, reported that survival was significantly worse in cases that were not located on the left side and were diagnosed at a more advanced stage. Wang et al.[18] also reported in their study, in which they examined the effect of colon cancer stage on survival, that survival status and duration were significantly lower in patients with colon cancer with a higher cancer stage. Our study determined that an increase in the colon cancer stage was associated with progression, progression-free survival, death, and overall survival. Considering that one of the purposes of cancer staging is to predict the prognosis, it is an expected result that a relationship was found between the cancer stage and survival. Survival is less in cases of more advanced colon cancer.

Another important variable in increasing or decreasing overall survival in cancer cases is progression development status. If progression has developed, the overall survival time of that case also decreases. In a comprehensive current systematic review and meta-analysis, Chowdhury et al.[19] evaluated 133 studies examining the relationship between progression development and overall survival in solid tumors and reported a high level of correlation between progression development and overall survival. In this study, the authors emphasized that progression development is essential in predicting overall survival in cancers. In our study, it was also determined that there was a relationship between the development of progression in colon cancer cases and death and overall survival time. In colon cancer, regular examination of the cases in terms of progression after diagnosis and initiation of the necessary treatment at the earliest period in cases with progression should be among the efforts to increase survival. Surgical resection is an essential part of the treatment of many solid tumors. Surgery can help patients recover from the disease and prolong their survival to a certain extent.[20] In a recent, comprehensive study examining national colorectal cancer registries in Denmark, England, Norway, and Sweden, Majano et al.[21] found that as the stage of colon and rectal cancers increased, the frequency of surgery decreased, and thus reported that survival was better in patients who underwent surgical resection. The study emphasized that colorectal cancer cases should be diagnosed early to perform surgery, which is known to have a significant impact on survival, and in this respect, the importance of regular screening of healthy individuals. In another recent study, Arhin et al.[22] examined the relationship between surgical resection and survival outcomes in young patients diagnosed with colorectal cancer and found that resection of both primary tumors and metastases separately increased survival in colorectal cancers independently of all other variables. It was found to increase the duration.

As emphasized in previous studies, one reason for this result in our study may be that the patients who underwent surgery consisted of earlier-stage patients. A patient with colon cancer at an earlier stage may have had a more prolonged survival because surgery was performed. Presumably, surgery and early stage were considered independent variables that

cumulatively increased survival. In the population thought to be healthy, early diagnosis and surgical treatment can be provided by regular colorectal cancer screening in line with the recommendations of current guidelines. With early diagnosis, surgical treatment and thus, survival can be increased.

The relationship of biomarkers examined in blood with cancer diagnosis and prognosis has been evaluated in many cancer types. A meta-analysis of studies investigating the prognostic value of pre-treatment CA 19-9 levels in colorectal cancer cases reported that CA 19-9 level is associated with overall survival and progression-free survival time and can predict mortality.[22-25]

The increase in CA 19-9 level is associated with the formation of tumor cell-induced platelet aggregation, a necessary process that plays a role in distant metastasis of colorectal cancer. It has been reported that CA 19-9 level recorded at diagnosis is a prognostic factor independent of other variables in metastatic colorectal cancers, it can predict bevacizumab efficacy and is associated with KRAS/BRAF mutation status. In our study, the deceased's CA 19-9 level was statistically significantly higher when compared to the survivors, which was consistent with these studies. Different mechanisms of CA 19-9 suggested in previous studies were thought to explain the relationship between pre-treatment serum CA 19-9 levels detected in our study and overall survival. Regarding the predictability of survival, it may be valuable to examine the value of CA 19-9 at the time of diagnosis.[26,27]

Much research has been and continues to be done on prognostic cancer markers. In these studies, several markers can be used to evaluate the survival of patients. It has been shown that electrolyte disturbance and systemic inflammation may be associated with the prognosis of various types of cancer. Serum sodium and globulin concentrations from routine laboratory tests were used as biochemical indicators. It has been stated that using serum sodium and globulin concentration alone is valuable in predicting clinical outcomes and survival in different malignancies and is inexpensive and easily accessible for routine blood tests. Electrolyte disturbance detected in patients with malignancy may indicate the development of any complication. Previous studies have suggested that low sodium, indicating the complication in cancer patients, may be associated with a poor prognosis.

Studies have also reported that serum sodium levels can decrease in approximately half of the cancer cases associated with a poor prognosis.[16] Sodium level in the lung, prostate, breast, and stomach It has been suggested that it may be associated with the presence and prognosis of different types of cancer.[15,28-32] In our study, serum sodium level at the beginning of the follow-up was low in 12 (8.6%) patients, but there was no correlation between the initial sodium level and the progression and survival times in colon cancer cases. No relationship was found. In our study, we only used the baseline sodium level; We did not consider the sodium change that occurred during the follow-up of the patients. Therefore, we did not associate sodium change with the development of complications and progression and survival times.

Globulin has a vital role in the immune system and inflammation. Functionally, it contains many proinflammatory proteins, including globulin, alpha1-globulin, and CRP.[17]

Elevated serum globulin levels have been associated with various chronic inflammatory diseases. However, the excess of inflammatory cells around the tumor has been found to be an accelerating parameter for tumor formation and proliferation. Similarly, an increase in hepatocyte-derived globulin levels has been shown following the inflammatory response. It has been reported that the pre-albumin/globulin ratio can predict the prognosis of colon cancer. Our study determined that serum globulin level at the beginning of follow-up in colon cancer cases was significantly negatively correlated with both progression-free and overall survival time. However, the change in serum globulin level during the follow-up period was not examined.

Among the biochemical parameters studied to predict the prognosis in colorectal cancers, the level of serum ALT, one of the liver enzymes, can be counted. In a study examining the relationship of this enzyme with progression in colorectal cancers, Scheipner et al. found a negative correlation between the increase in ALT and progression-free and overall survival.[32] Jiang et al.[33] reported that the increase in ALT was associated with liver metastasis and, thus, a worse prognosis in colorectal cancer cases. In a similar study, Park et al.[34] also showed that liver volume and liver function tests were negatively associated with survival in patients with colorectal cancer. Similarly, our study found that serum ALT level at the beginning of follow-up in colon cancer cases was negatively correlated with progression-free and overall survival time. As suggested in previous studies, the increase in serum ALT levels of the patients might have affected their survival of liver metastasis and functionality.

Limitations of the Study

This study, performed on patients with colon cancer cases in our center for a certain period, has some limitations. The significant limitations of the study are its retrospective and single-center design and lack of case studies. In the study, it was researched only whether these values could predict the prognosis of colon cancer. The other limitation is due to its retrospective design, its unable to obtain the monitoring process of sodium globulin level and sodium/globulin ratios and different parameters affecting them since our single-centered study represents the results of cases only in a particular region. Even though the clinical status of cases at the moment of diagnosis is known, The time elapsed between the initial onset of the disease and the diagnosis may differ between patients. this situation may have affected the biochemical parameters of the cases in different stages colon cancer in this study. In our study, the biochemical values at the beginning of the follow-up were considered. The variance of level during follow-up may have positively or negatively affected progression and survival.

CONCLUSION

It was concluded that the initial sodium/ globulin ratio and globulin level of the patients diagnosed with colon cancer was a weak correlation with a progression-free and overall survival time; However, it has been determined to be not predictive of progression and survival. By researching different parameters that may affect sodium and globulin levels in more cases, the correlation and mechanism of the relationship between sodium and globulin levels between malignancies can be revealed in more detail. Our results should be interpreted with these limitations in mind..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-invasive Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021.06.14).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Xiao JB, Leng AM, Zhang YQ, Wen Z, He J, Ye GN. CUEDC2: multifunctional roles in carcinogenesis. *Front Biosci (Landmark Ed).* 2019;24(5):935-946. doi:10.2741/4759
2. Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis. *Dis Mon.* 2019;65(12):100851. doi:10.1016/j.disamonth.2019.02.004
3. Sokic-Milutinovic A. Appropriate management of attenuated familial adenomatous polyposis: report of a case and review of the literature. *Dig Dis.* 2019;37(5):400-405. doi:10.1159/000497207
4. Allen J, Sears CL. Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: contributions to colorectal cancer development. *Genome Med.* 2019;11(1):11. doi:10.1186/s13073-019-0621-2
5. Snyder C, Hampel H. Hereditary colorectal cancer syndromes. *Semin Oncol Nurs.* 2019;35(1):58-78. doi:10.1016/j.soncn.2018.12.011
6. Célind J, Ohlsson C, Bygdell M, Nethander M, Kindblom JM. Childhood body mass index is associated with risk of adult colon cancer in men: an association modulated by pubertal change in body mass index. *Cancer Epidemiol Biomarkers Prev.* 2019;28(5):974-979. doi:10.1158/1055-9965.EPI-18-1077
7. Pedersen JK, Rosholm JU, Ewertz M, Engholm G, Lindahl-Jacobsen R, Christensen K. Declining cancer incidence at the oldest ages: Hallmark of aging or lower diagnostic activity?. *J Geriatr Oncol.* 2019;10(5):792-798. doi:10.1016/j.jgo.2019.02.001
8. Batool R, Jamal K, Sheroze MW, et al. Clinical features of colorectal carcinoma at the Jinnah Postgraduate Medical Centre, Karachi, Pakistan: a cross-sectional study. *J Med Res Health Sci.* 2022;5(9):2203-2209. doi: 10.52845/JMRHS/2022-5-9-1
9. T.C. Sağlık Bakanlığı Türkiye Halk Sağlığı Kurumu Türkiye Kanser İstatistikleri, Ankara 2017. [Internet] https://hsgm.saglik.gov.tr/tr/kanser-istatistikleri. Erişim: 14.8.21.
10. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. *Ann Afr Med.* 2019;18(3):121-126. doi:10.4103/aam.aam_56_18
11. Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance. *World J Gastroenterol.* 2019;25(31):4383-4404. doi:10.3748/wjg.v25.i31.4383
12. Rosner MH, Dalkin AC. Electrolyte disorders associated with cancer. *Adv Chronic Kidney Dis.* 2014;21(1):7-17. doi:10.1053/j.ackd.2013.05.005
13. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. *Am J Kidney Dis.* 2012;59(2):222-228. doi:10.1053/j.ajkd.2011.08.029
14. Zhang L, Wang Z, Xiao J, et al. Sodium to globulin ratio as a prognostic factor for patients with advanced gastric cancer. *J Cancer.* 2020;11(24):7320-7328. doi:10.7150/jca.47314
15. Lopes G, Stern MC, Temin S, et al. Early detection for colorectal cancer: ASCO Resource-Stratified Guideline. *J Glob Oncol.* 2019;5:1-22. doi:10.1200/JGO.18.00213
16. Chen W, Xin S, Xu B. Value Research of NLR, PLR, and RDW in prognostic assessment of patients with colorectal cancer. *J Healthc Eng.* 2022;2022:7971415. doi:10.1155/2022/7971415
17. Ulanja MB, Rishi M, Beutler BD, et al. Colon cancer sidedness, presentation, and survival at different stages. *J Oncol.* 2019;2019:4315032. doi:10.1155/2019/4315032
18. Wang L, Wilson SE, Stewart DB, Hollenbeak CS. Marital status and colon cancer outcomes in US Surveillance, Epidemiology and End Results registries: does marriage affect cancer survival by gender and stage?. *Cancer Epidemiol.* 2011;35(5):417-422. doi:10.1016/j.canep.2011.02.004
19. Chowdhury S, Mainwaring P, Zhang L, et al. Systematic review and meta-analysis of correlation of progression-free survival-2 and overall survival in solid tumors. *Front Oncol.* 2020;10:1349. doi:10.3389/fonc.2020.01349
20. Peach G, Kim C, Zacharakis E, Purkayastha S, Ziprin P. Prognostic significance of circulating tumour cells following surgical resection of colorectal cancers: a systematic review. *Br J Cancer.* 2010;102(9):1327-1334. doi:10.1038/sj.bjc.6605651
21. Benitez Majano S, Di Girolamo C, Rachet B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. *Lancet Oncol.* 2019;20(1):74-87. doi:10.1016/S1470-2045(18)30646-6
22. Arhin ND, Shen C, Bailey CE, et al. Surgical resection and survival outcomes in metastatic young adult colorectal cancer patients. *Cancer Med.* 2021;10(13):4269-4281. doi:10.1002/cam4.3940
23. Yu Z, Chen Z, Wu J, Li Z, Wu Y. Prognostic value of pretreatment serum carbohydrate antigen 19-9 level in patients with colorectal cancer: A meta-analysis. *PLoS One.* 2017;12(11):e0188139. doi:10.1371/journal.pone.0188139
24. Stokkel LE, van Rossum HH, van de Kamp MW, et al. Clinical value of preoperative serum tumor markers CEA, CA19-9, CA125, and CA15-3 in surgically treated urachal cancer. *Urol Oncol.* 2023;S1078-1439(23)00045-5. doi:10.1016/j.urolonc.2023.01.018
25. Basbug M, Arikanoglu Z, Bulbuller N, et al. Prognostic value of preoperative CEA and CA 19-9 levels in patients with colorectal cancer. *Hepatogastroenterology.* 2011;58(106):400-405.
26. Narita Y, Taniguchi H, Komori A, et al. CA19-9 level as a prognostic and predictive factor of bevacizumab efficacy in metastatic colorectal cancer patients undergoing oxaliplatin-based chemotherapy. *Cancer Chemother Pharmacol.* 2014;73(2):409-416. doi:10.1007/s00280-013-2367-7
27. Martini F, Guadagni F, Lenti L, et al. CA 19-9 monosialoganglioside content of human colorectal tumor cells correlates with tumor cell-induced platelet aggregation. *Anticancer Res.* 2000;20(3A):1609-1614.
28. Sun DW, An L, Lv GY. Albumin-fibrinogen ratio and fibrinogen-prealbumin ratio as promising prognostic markers for cancers: an updated meta-analysis. *World J Surg Oncol.* 2020;18(1):9. doi:10.1186/s12957-020-1786-2
29. Hara K, Aoyama T, Yamada T, et al. The prognostic value of the perioperative systemic inflammation score for patients with advanced gastric cancer. *Anticancer Res.* 2020;40(3):1503-1512. doi:10.21873/anticanres.14095
30. Xu J, Chen X, Wang X, et al. Preoperative hyponatremia and hypocalcemia predict poor prognosis in elderly gastric cancer patients. *Cancer Manag Res.* 2019;11:8765-8780. doi:10.2147/CMAR.S211603
31. House CD, Vaske CJ, Schwartz AM, et al. Voltage-gated Na+ channel SCN5A is a key regulator of a gene transcriptional network that controls colon cancer invasion. *Cancer Res.* 2010;70(17):6957-6967. doi:10.1158/0008-5472.CAN-10-1169
32. Scheipner L, Smolle MA, Barth D, et al. The AST/ALT ratio is an independent prognostic marker for disease-free survival in stage II and III colorectal carcinoma. *Anticancer Res.* 2021;41(1):429-436. doi:10.21873/anticanres.14792
33. Jiang Z, Li C, Zhao Z, et al. Abnormal liver function induced by space-occupying lesions is associated with unfavorable oncologic outcome in patients with colorectal cancer liver metastases. *Biomed Res Int.* 2018;2018:9321270. doi:10.1155/2018/9321270
34. Park JS, Park HC, Choi DH, et al. Prognostic and predictive value of liver volume in colorectal cancer patients with unresectable liver metastases. *Radiat Oncol J.* 2014;32(2):77-83. doi:10.3857/roj.2014.32.2.77